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Epidemiology of septo-optic dysplasia with focus on prevalence and maternal age – A EUROCAT study

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Abstract

Septo-optic nerve dysplasia is a rare congenital anomaly ~~known to be caused by a midline developmental defect in the prosencephalon~~ with optic nerve hypoplasia, pituitary hormone deficiencies and midline developmental defects of the brain. The clinical findings are visual impairment, hypopituitarism and developmental delays. ~~and severity is related to the extent of the cerebral anomalies in the septum pellucidum, optic nerves and hypothalamus~~. The aim of this study was to report prevalence, associated anomalies, maternal age and other epidemiological factors from a large European population based network of congenital anomaly registries (EUROCAT). Data from 29 full member registries for the years 2005-2014 were included, covering 6.4 million births. There were 99 cases with a diagnosis of septo-optic dysplasia. The prevalence of septo-optic dysplasia in Europe was calculated to lie between 1.9 and 2.5 per 100,000 births after adjusting for potential under-reporting in some registries. The prevalence was highest in babies of mothers aged 20 to 24 years of age and was significantly higher in UK registries compared with other EUROCAT registries (P = 0.021 in the multilevel model) and the additional risk for younger mothers was significantly greater in the UK compared to the rest of Europe (P=0.027). The majority of septo-optic dysplasia cases were classified as an isolated cerebral anomaly (N = 76, 77%) ~~and only two cases had a genetic diagnosis~~. Forty percent of diagnoses occurred in fetuses with a prenatal diagnosis. The anomaly may not be visible at birth, which is reflected in that 57% of the postnatal diagnoses occurred over 1 month after birth.

This is the first population based study to describe the prevalence of septo-optic dysplasia in Europe. Septo-optic dysplasia shares epidemiological patterns with gastroschisis and this strengthens the hypothesis of vascular disruption being an aetiological factor for septo-optic dysplasia.

Key words:

Septo-optic dysplasia, prevalence, population based, maternal age, associated anomalies, EUROCAT

Introduction

Septo-optic nerve dysplasia is a rare congenital anomaly, described for the first time in 1941 (Reeves 1941) with optic nerve hypoplasia, pituitary hormone deficiencies and midline developmental defects of the brain (anomalies of septum pellucidum and/or corpus callosum) ~~and now known to be caused by a midline developmental defect in the prosencephalon~~ (Webb and Dattani 2010). The clinical findings are visual impairment, hypopituitarism and developmental delay~~s~~. Severity of developmental delay ~~is~~ seems to be related to the extent of the cerebral anomalies in the septum pellucidum, optic nerves and hypothalamus (Fard et al 2010) and to complications to the disease (Khaper et al 2017). The cerebral anomalies that are part of septo-optic dysplasia may be diagnosed prenatally by ultrasound. Cases with associated major anomalies may be diagnosed at birth, while others appear later in infancy or childhood with the diagnosis of vision disability and growth failure leading to a final diagnosis of septo-optic dysplasia (Webb and Dattani 2010).

There are very few epidemiological studies of septo-optic nerve dysplasia and therefore the prevalence is uncertain, but a study from the North West of England reported a prevalence of 5.4 per 100,000 births (Patel et al 2005) and a study from the West Midlands of England reported a prevalence of 3.5 per 100,000 births (Atapattu et al 2012). Most cases are sporadic and only a few cases have a genetic aetiology (Fard et al 2010, Webb and Dattani 2010). There is no sex difference reported, but an association with young maternal age has been reported (Webb and Dattani 2010). It has been proposed that the anomaly septo-optic dysplasia should be classified as a heterogeneous malformation syndrome or septo-optic dysplasia complex rather than a precisely defined entity (Polizzi et al 2006). Another hypothesis is that septo-optic dysplasia is a vascular disruption sequence (Lubinsky 1997, Stevens and Dobyns 2003), with the same aetiology as that for hydranencephaly, gastroschisis, small intestinal atresia, terminal limb reductions and Poland anomaly (van Gelder et al 2010).

The aim of this study is to report the prevalence, maternal age, associated anomalies and other epidemiological factors from a large European population-based network of congenital anomaly registries in the ten-year period 2005-2014.

Methods

EUROCAT Data Collection

EUROCAT is a European network of population-based congenital anomaly registries and currently provides the most complete data on congenital anomalies occurring in Europe. EUROCAT was established in 1979 and currently 33 registries in 18 countries provided information on individual cases from 2005-2014 arising from seven million births. The European Union has provided funding for a central registry to coordinate the network, and the member registries are funded locally by national or regional governments, research or other bodies. All EUROCAT registries are population based and have a defined geographical coverage. All births from mothers resident within the defined geographical area are covered by the registries ~~: in some countries all births are covered by a registry (for example Malta and Norway) and in other countries less than 10% of that country's birth population are covered by a registry (for example Denmark, Germany and Ukraine).~~

All EUROCAT registries use multiple sources of information to ascertain cases in live births, late fetal deaths (≥20 weeks gestation), and terminations of pregnancy for fetal anomaly (TOPFA) at any gestational age. Data sources, depending on registry, include maternity, neonatal, and paediatric records; fetal medicine, cytogenetics, pathology, and medical genetics records; specialist services including paediatric cardiology; and hospital discharge and child health records. The EUROCAT central database is hosted by the European Commission Joint Research Centre in Ispra, Italy. Registries submit individual anonymised records of cases of congenital anomalies. All cases are coded to the International Classification of Diseases (ICD) version 10 with 1-digit British Paediatric Association (BPA) extension. Each case can have one syndrome code and up to eight malformation codes. All coding is standardised by using the EUROCAT guide (version 1.4) with isolated minor anomalies, e.g. skin tags, being excluded (EUROCAT website).

All full member EUROCAT registries were invited to the study and ~~D~~data from 29 EUROCAT registries for the years 2005-2014 were included. Twenty-five of the 29 registries registered all anomalies diagnosed in infants presenting up to at least the age of one year and nine of these registries included cases presenting up to 5 years of age or more. Four registries included cases diagnosed in the first week or the first month after birth. Inclusion criteria for this study were all cases coded with the ICD10 code Q044 for septo-optic dysplasia. Cases were classified as isolated cerebral anomalies, chromosomal cases, teratogenic or genetic syndromes or multiple congenital anomalies according to the EUROCAT multiple flowchart (Garne et al 2011) and manual review of the written text description of the anomalies by one of the authors. Cases with isolated cerebral anomalies were further classified as septo-optic dysplasia only and associated major cerebral anomalies. There were no written text descriptions for cases from two registries.

Statistical Analysis

Method to Identify Under-reporting

There was evidence that some registries were under-reporting cases of septo-optic dysplasia. For example, three large registries each covering over 200,000 births reported no cases of septo-optic dysplasia. There is no objective measure that would identify in which registries there is under-reporting of this specific anomaly. Therefore, the following method was used to predict the expected prevalence: the average prevalence in the 15 registries with the highest prevalences can be calculated. There are two possible extreme scenarios:

a) these registries really do have the highest prevalences and, although there is some under-reporting the other registries, do not have such high prevalences

b) these registries do NOT have the highest prevalences and under-reporting in all the other registries would mean that they, with good reporting, would also have a similar prevalence to the chosen 15 registries.

If (b) is correct then the prevalence estimated from the 15 registries would be an unbiased estimate of the average for all registries. If (a) is correct, then the average prevalence of the whole population can be estimated by adjusting the prevalence observed in these 15 registries by a factor to adjust for the fact that these registries have the highest prevalence estimate amongst 29 registries. This factor was estimated to be 1.35; obtained by simulation and calculation of the ratio of the mean prevalence of 15 out of 29 registries compared to the mean prevalence of all 29 registries assuming the number of cases is a Poisson distribution with an expected value of five cases (the median observed number of cases in the 15 registries). The average prevalence in the 15 registries was estimated by using a random effects model. All registries whose upper confidence interval for their estimated prevalence was below the estimated limit of true prevalence were then excluded when calculating the prevalence of septo-optic dysplasia according to maternal age.

The prevalence of septo-optic dysplasia according to maternal age was estimated using a multi-level random effects Poisson model, to adjust for registry, and maternal age as a categorical variable with the following categories (15-19, 20-24, 25-29, 30-34, ≥ 35). An additional model including being from the UK and a UKxAge interaction was also fitted. This sensitively analysis was carried out as, from previous studies, it was expected that fetuses of younger mothers would have a higher risk of septo-optic dysplasia (Elster and McAnarney 1979, Lippe 1979, Murray et al 2005, Atapattu et al 2012). This is unusual and the other main anomaly in which this age-related risk is seen is gastroschisis (Loane et al 2009). Gastroschisis has a high prevalence in younger mothers in the UK compared to

the rest of Europe (Loane et al 2007). Therefore, it was aimed to investigate if a similar difference occurs for septo-optic dysplasia.

Results

Prevalence

There were 99 cases with a diagnosis of septo-optic dysplasia in the 29 EUROCAT registries. The overall prevalence in the top 15 registries was 2.51 per 100,000 births (95%CI: 1.60-3.58), with clear evidence of heterogeneity; I^2=59.9%. If there was no under-reporting the estimated prevalence for all registries would be 2.51/1.35 (factor determined by simulation) = 1.9 per 100,000 births with 95% CI approximately 1.2 - 2.6. The prevalence is therefore likely to lie between 1.9 and 2.5 per 100,000 births. The following seven registries were judged to have evidence of under-reporting as their upper 95% CI for their country prevalence was below 1.9 per 100,000 births: Antwerp, South Portugal, Tuscany, Paris, Valencia Region, Emilia Romagna and Norway. Figure 1 shows the prevalence of septo-optic dysplasia in the remaining 22 registries.

There was no evidence of any change in prevalence from 2005 to 2014 (data not shown).

Maternal age

Figure 2 shows the prevalence of septo-optic dysplasia according to maternal age at birth for the 22 registries. The prevalence was highest for mothers aged 20 to 24 years of age. Figure 3 shows that the prevalence of septo-optic dysplasia is significantly higher in UK registries compared with the other EUROCAT registries (p = 0.021 in the multilevel model) and the increase was greatest for younger mothers (20-24 years) in the UK (p = 0.027).

Clinical data

Table 1 shows that 96% of the 99 cases were live births and 4% resulted in a TOPFA. There were similar numbers of males and females. There was a high proportion of preterm birth (18%), but also 8% born with gestational age ≥ 42 weeks. Age at diagnosis was known for 85 cases. Forty percent of these ~~cases~~ were diagnosed prenatally, 25% were diagnosed within 1 month of birth and further 29% were diagnosed within the first year of life (Table 1).~~.~~ ~~For postnatally diagnosed cases, more than 50% were diagnosed later than one month of birth~~.

~~Table 2 describes the classification of isolated and associated anomalies for the 99 cases: 76 were classified as isolated cerebral anomaly, two had a genetic diagnosis (Down syndrome and Mowat-Wilson syndrome), one a teratogenic exposure (congenital CMV infection) and 20 had associated non-cerebral major anomalies. The most frequent associated anomalies were congenital heart defects (40%), congenital limb anomalies and congenital eye anomalies (20% each). The four cases with associated eye anomalies had anophthalmos, microphthalmos, glaucoma and coloboma of eyelid with corneal opacity.~~

Table 2 describes the classification of the 99 cases: 73 cases were classified as isolated cerebral anomaly with 48 having septo-optic dysplasia only and 25 cases with associated major cerebral anomalies. There were 23 cases with associated major con-cerebral anomalies and one case each classified as chromosomal anomaly (Down syndrome), genetic syndrome (Mowat-Wilson) and teratogenic syndrome (maternal CMV infection). The associated anomalies are presented in Table 3 with schizencephaly as the most frequent cerebral anomaly and VSD and microphthalmos as the most frequent non-cerebral anomalies. There were two cases with limb reduction defects and one case with gastroschisis.

Discussion

The prevalence of septo-optic dysplasia in the EUROCAT registries was calculated to be between 1.9 and 2.5 per 100,000 births. To our knowledge, there are only three ~~two~~ previous published population-based studies with data on the prevalence of septo-optic dysplasia. The first study from the NorthWest of England estimated the prevalence of septo-optic dysplasia to be of 5.4 per 100,000 births (Patel et al 2006). The estimate by Patel et al is a prevalence of 10.9 per 100,000 births for optic nerve hypoplasia and they stated that 50% of these cases had septo-optic dysplasia. The second study based in the West Midlands of England estimated a prevalence of 3.5 per 100,000 births (Atapattu et al 2012). The estimate in this paper is a prevalence of 8.3 per 100,000 births calculated by comparing the 88 cases of septo-optic dysplasia occurring in children under 16 diagnosed from 1998 to 2009 with the births that occurred from 1998 to 2009. However this ignores the fact that all children up to the age of 16 were included in the study from 1998 onwards – these children could have been born up to 15 years before 1998 i.e. from 1983. Therefore, all births from 1983 to 2009 need to be included in the calculation of prevalence. From publications from the UK Office for National Statistics this is approximately 2.5 million births giving a prevalence of 88/2.5 million = 3.5 per 100,000 births. A third study from Canada reported a prevalence of 53 per 100,000 from 2011 to 2016, observing an 800% increase over the previous 20 years (Khaper et al 2017). They also observed clustering occurring with some Federal Electoral Districts having rates ten times higher than other districts. The data in our study are consistent with the prevalence of septo-optic dysplasia in the early part of the Canadian study and later inconsistencies may be due to specific increases occurring in Canada that have not been observed in Europe.

Considering the observed higher prevalence in the UK registers in our study, the overall European estimate of between 1.9 and 2.5 per 100,000 births obtained in this current analysis seems reasonable. A Swedish national study of risk factors for optic nerve hypoplasia described 13 cases of septo-optic dysplasia in 1979-97 in a total birth population of 2,109,316 giving a prevalence of 0.6 per 100,000 births (Tornqvist et al 2002). The entry to the study was a registration in the Swedish Register of Visually Impaired Children and less than 25% of the children with septo-optic dysplasia have significant visual impairment (Webb and Dattani 2010). Taking this into account would suggest that the overall prevalence of septo-optic dysplasia was about 2.4 per 100,000 births, which is commensurate with the estimate in the current study reported here.

Our study also observed the association of lower maternal age and increased risk of septo-optic dysplasia, which has been noted in several studies (Elster and McAnarney 1979, Lippe et al 1979,

Murray et al 2005, Khaper et al 2017). There are only a few congenital anomalies that are associated with younger maternal age, with gastroschisis having the strongest association (Loane et al 2009). As we have shown for septo-optic dysplasia, the prevalence of gastroschisis is also higher in the UK compared to continental Europe (Loane et al 2007) and the aetiology is considered to be a result of a vascular disruption (van Gelder et al 2010). This study included one septo-optic dysplasia case associated with gastroschisis from a UK registry and further two cases had associated limb reduction defects. There are three published cases reports with septo-optic dysplasia and gastroschisis diagnosed together from Australia and US (Kamien et al 2010, Jordan and Montezuma 2015, Garvin et al 2016). The hypothesis of septo-optic dysplasia being a vascular disruption sequence was published by Lubinsky in 1997. Our results support this hypothesis with the higher prevalence in the UK also for young maternal age and the low proportion of genetic cases.

There was a high proportion of cases born preterm (18%). A Canadian study found that 26/50 (52%) were born preterm (Khaper). Others have reported a median gestational age to be 40.0 ± 0 (Riedl et al 2008) for 30 patients with septo-optic dysplasia referred to their center for treatment. In general, the presence of a congenital anomaly in the fetus increases the risk of preterm birth (Kase and Visintainer 2007) and in Europe the overall rate of preterm birth ranged from 6-11% in 2008 (Zeitlin et al 2013).

Forty percent of our cases were diagnosed prenatally and further 54% were diagnosed before the age of one year. ~~for those diagnosed postnatally, age at diagnosis was more than one month for the majority of cases~~. The median age at diagnosis is therefore likely to be around 2 months, less than reported in the Canadian study that found a median age at diagnosis for septo-optic dysplasia with or without associated cerebral anomalies at 8.5 and 7.5 months (Khaper et al 2017). The cerebral anomalies in the septum pellucidum and the associated major cerebral anomalies can be diagnosed by prenatal ultrasound examination and most European countries offer a prenatal ultrasound screening of major fetal anomalies in the second trimester of pregnancy. If the newborn infant with septo-optic dysplasia has no visible anomalies at birth, the postnatal diagnosis will most likely be made when concerns about vision impairment or endocrine abnormalities arise weeks or months after birth.

The strength of our study is the large European population covered over a defined time period of 10 years and a population of 6.4 million births. All registries used the same standard methodology of case ascertainment and case classification. It is a limitation that some registries may have under-reporting of septo-optic dysplasia. However, the simple robust method of analysis adopted adjusted for this under-reporting in estimating the prevalence. Not all registries include cases diagnosed with

an anomaly after one month of age and not all have active follow-up of diagnosis after an initial suspected diagnosis at birth. There may be cases in our large population that were diagnosed prenatally or at birth with a cerebral anomaly, but with the additional diagnosis of septo-optic dysplasia diagnosed later in infancy or childhood which has not been reported to the relevant registry.

Conclusions.

This is the first population-based study to describe the prevalence of septo-optic dysplasia in Europe and the largest described cohort. Our study shows that the prevalence is higher in the UK compared to continental Europe. We also confirmed previous findings of younger maternal age as a risk factor. Septo-optic dysplasia shares epidemiological patterns with gastroschisis and this strengthens the hypothesis of vascular disruption being an aetiological factor for septo-optic dysplasia.

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Table 1: Characteristics of 99 cases of septo-optic dysplasia. EUROCAT registries 2005-2014

Anomaly		Septo-optic dysplasia
Total Number		99
Prevalence per 100,000 births		1.9 to 2.5
Live births Number (%)		95 (96)
Fetal Deaths Number (%)		0 (0)
TOPFA Number (%)		4 (4)
Maternal age (years) (95% CI)		23.4 (22.3 – 24.5)
Timing of Diagnosis (14 cases with unknown if pre or postnatal and 9 postnatal with unknown timing)	Prenatal diagnosis (% of 85 known diagnoses)	34 (40%)
	At birth (% of 42 known postnatals)	10 (24%)
	Within 1 month (% of 42 known postnatals)	8 (19%)
	1-12 months (% known postnatals)	20 (48%)
	Over 12 months (% of 42 known postnatals)	4 (9%)
Percentage Male (95% CI)		55 % (45-65)
Gestational Age at livebirth (95 livebirths, 2 cases with missing gestational age)	< 37 weeks (%)	17 (18%)
	37-41 weeks (%)	69 (74%)
	≥ 42 weeks (%)	7 (8%)
Birthweight (kg)	< 37 weeks (95% CI)	1.77 (1.4 – 2.1)
	37-41 weeks (95% CI)	3.18 (3.0 – 3.3)
	≥ 42 weeks (95% CI)	3.76 (3.4 – 4.1)

Anomaly	Septo-optic dysplasia
Total Number	99
Prevalence per 100,000 births	1.9 to 2.5
Live births Number (%)	95 (96)
Fetal Deaths Number (%)	0 (0)
TOPFA Number (%)	4 (4)

Maternal age (years) (95% CI)		23.4 (22.3 – 24.5)
Timing of Diagnosis (14 cases with unknown if pre or postnatal and 9 postnatal with unknown timing)	Prenatal diagnosis (% of 85 known diagnoses)	34 (40%)
	At birth (% of 42 known postnatals) [% of all diagnoses]	10 (24%) [14%]†
	Within 1 month (% of 42 known postnatals) [% of all diagnoses]	8 (19%) [11%] †
	1-12 months (% known postnatals[% of all diagnoses])	20 (48%) [29%] †
	Over 12 months (% of 42 known postnatals) [% of all diagnoses]	4 (9%) [6%] †
Percentage Male (95% CI)		55 % (45-65)
Gestational Age at livebirth (95 livebirths, 2 cases with missing gestational age)	< 37 weeks (%)	17 (18%)
	37-41 weeks (%)	69 (74%)
	≥ 42 weeks (%)	7 (8%)
Birthweight (kg)	< 37 weeks (95% CI)	1.77 (1.4 – 2.1)
	37-41 weeks (95% CI)	3.18 (3.0 – 3.3)
	≥ 42 weeks (95% CI)	3.76 (3.4 – 4.1)

† : Percentage of all diagnoses is % of postnatal diagnoses with known timing x (1-% prenatal diagnoses) ie x 60%

Table 2. Classification of 99 septo-optic dysplasia cases according to associated anomalies and genetic diagnosis. EUROCAT registries 2005-2014

	~~Total (n=99)~~	~~%~~
	~~Number~~	~~%~~
~~Isolated cerebral anomaly~~	~~76~~	~~76~~
~~Chromosomal~~	~~1~~	~~1~~
~~Genetic syndrome~~	~~1~~	~~1~~
~~Teratogenic syndrome including maternal infections~~	~~1~~	~~1~~
~~Multiple congenital anomaly~~	~~20~~	~~20~~
~~- Multiple with congenital heart defects~~	~~8~~	~~8~~
~~- Multiple with congenital limb anomalies~~	~~4~~	~~4~~
~~- Multiple with congenital renal anomalies~~	~~0~~	~~0~~
~~- Multiple with congenital eye anomalies~~	~~4~~	~~4~~
~~- Multiple with gastroschisis~~	~~1~~	~~1~~

Classification	**Number**	**% of total**
Septo-optic dysplasia only	**48**	48
Other Cerebral anomalies	**25**	25
Multiple congenital anomalies	**23**	23
Chromosomal	**1**	1
Genetic syndrome	**1**	1
Teratogenic/maternal infection	**1**	1
Total	**99**	

Table 3. Associated major congenital anomalies diagnosed in 51 of 99 septo-optic dysplasia cases. EUROCAT registries 2005-2014

Associated anomalies[1]	Numbers	% of ?
Cerebral		
Schizencephaly	12	
Holoprosencephaly	6	
Agenesis of corpus callosum	7	
Polymicrogyria	4	
Cardiac		
VSD	4	
Patent ductus	2	
Pulmonary valve stenosis	2	
Eye		
Microphthalmos	4	
Coloboma	3	
Anophthalmos	1	
Glaucoma	1	
Limb		
Limb reduction defects	2	
Club foot	1	
Hip dislocation	1	
Facial clefts		
Cleft lip and palate	2	
Cleft palate	1	
Gastrointestinal		
Gastroschisis	1	

[1]a case may have more than one anomaly